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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/981,583	02/03/98	DICKMANNS	A 028622/0/0

HM22/1022

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EXAMINER	
HARRIS, A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/981,583	Applicant(s) DICKMANNS ET AL.	
	Examiner Alana M. Harris, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,16-22,29-31,33-35 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,16-22,29-31,33-35 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Claims 1-12, 16-22, 29-31, 33-35 and 38 are pending.

Claim 1 has been amended.

Claims 1-12, 16-22, 29-31, 33-35 and 38 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claim Rejections - 35 U.S.C. § 103

3. The rejection of claims 1-10, 16-22 and 38 under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985), in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) is withdrawn in view of Applicants' amendment to claim 1.

4. The rejection of claims 1-12, 16-22, 29, 30 and 38 under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985) in view of Garcia et

al.(Molecular and Cellular Biology 6(6):1974-1982) and Blankenstein et al. (Current Biology 3:694-698, 1991) is withdrawn in light of Applicants' amendment to claim 1.

5. The rejection of claims 1-10, 16-22, 31 and 38 under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985), in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Sigma Cell Culture Catalogue and Price List (1995) is withdrawn in view of Applicants' amendment to claim 1.

6. The rejection of claims 1-10, 16-22, 33, 34 and 38 under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985), in view Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Gottlinger et al. (Int. J. Cancer 38:47-53, 1986) is withdrawn in light of Applicants' amendment to claim 1.

New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 103

7. Claims 1-10, 16-22 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Chang (Biochimica et Biophysica Acta 823:161-194, 1986). Ohnuki teaches disseminated human prostatic adenocarcinoma tumor cell lines (see

Abstract and Materials and Methods section of page 524). These autologous cells with metastatic potential are derived from bone marrow (see Abstract, paragraph 2; page 524, column 2, first full paragraph and Materials and Methods section, paragraph 2). Ohnuki does not teach the said cell has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA in its genome nor at least one additional oncogene. Additionally, Ohnuki does not teach at least one defect in the origin of replication or the *in vitro* process by which the tumor cell incorporates the DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell. Ohnuki lacks the method step of incorporating DNA via microinjection, which is performed after the step of carrying out a primary expansion of said epithelial tumor cells comprising the step of culturing in a medium with epidermal growth factor on the extracellular matrix, collagen coated tissue flasks.

However, Garcia does teach an autologous, disseminated immortalized rabbit mammary epithelial tumor cell which has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA. The epithelial tumor cell contains at least one defect in the origin of replication. Garcia also teaches an epithelial tumor cell that has integrated in its genome at least one additional oncogene, wherein the additional oncogene is c-Ha-ras. Garcia continues to teach the *in vitro* process by which the tumor cell incorporated the DNA encoding at least one immortalizing oncogene. The step of incorporating DNA comprising microinjection, which was performed after the step of carrying out a primary expansion of said epithelial tumor cells. The primary expansion comprised the step of

culturing in a medium comprising epidermal growth factor on the extracellular matrix, collagen coated tissue flasks.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the cell lines of Ohnuki to establish a metastatic cell lines suitable for studying the immortalizing and transforming potential of known and candidate genes for epithelial cells. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Ohnuki, Garcia and Chang that the establishment of such cell lines could be readily made and successfully propagated in order to conduct experiments geared to the long term study of metastasis in many assay systems. Chang states on page 163, column 1, first full paragraph that "[b]esides the obvious use of human epithelial cell *in vitro* to study multistage carcinogenesis ...[these] immortalized lines ...are invaluable, since they can be used for studying epithelial cell biology, especially differentiation. In addition the lines can used to generate monoclonal antibodies...". Clearly since 1986 "[t]ransformation of mammalian cells in vitro by SV40 is a widely used experimental model for studying viral oncogenesis...", as well as the art known reason to this approach is for scientist to characterize genetic and epigenetic modifaication that occur during tumorigenic stages in cells which maintain the phenotypic characteristics of their tissue of origin. Cancer research studies require the use of cells that do not undergo limited proliferation or senescence. These cell lines are quite useful for research on causes, treatment and prevention of cancer.

Applicants argued in the response filed August 13, 2001 (Paper number 24) as well as previous response that "Garcia does not disclose the transformation of a tumor cell but rather the transformation of a normal epithelial cell, and therefore the immortalization of a non-tumor cell." Applicants also argue how Garcia states that with the combination of SV40 DNA and activated c-Ha-ras gene that drastic changes were seen in the micro-injected cells SV40 viral DNA and/or the human oncogene Ha-ras." This is found unpersuasive for the reasons stated above, as well as the fact that the claims of the instant invention are drawn to a product and not a method of making the claimed product. Garcia provides a protocol that successfully those skilled in the art to establish a continuous tissue culture line, which would be useful for research *in vitro*. The multifactorial causes of cancer have yet to be totally discovered so it is necessitated that immortalized cell lines be used as a unique *in vitro* model system for analysis of molecular events underlying carcinogenesis.

8. Claims 1-12, 16-22, 29, 30 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980) in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), Blankenstein et al. (Current Biology 3:694-698, 1991) and Chang (Biochimica et Biophysica Acta 823:161-194, 1986). The teachings of Ohnuki of an epithelial tumor cell lines with metastatic potential, Garcia of methodology to immortalize, incorporate DNA and culturing said cell and Chang have been discussed in the paragraphs above. These references do not teach the epithelial tumor cell having integrated in its

genome or another replicative genetic element an externally introduced gene encoding a cytokine immunostimulatory factor, such as interleukin-4 (IL-4).

However, Blankenstein et al. teach the transfer of single cytokine genes into cancer cells. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention was made to introduce genes encoding cytokine immunostimulatory factors, such as IL-4, granulocyte colony-stimulating factor and tumor necrosis factor into the tumor cells of Ohnuki. One of ordinary sill in the art would have been motivated to do so with a reasonable expectation of success by the teachings well known in the art, that the transfer and the expression of such immunostimulatory factor genes into cancer cells would mediate powerful tumor suppression potential in T-cell deficient animals and appear to be effective even for poorly or non-antigenic tumors. Additionally, Blankenstein et al. report that "cancer cells transfected to produce certain cytokines might induce effective tumor-specific immunity in cancer patients".

9. Claims 1-10, 16-22, 31 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), Chang (Biochimica et Biophysica Acta 823:161-194, 1986) and Sigma Cell Culture Catalogue and Price List (1995). The teachings of Ohnuki and Garcia of production of a cultured immortalized metastatic epithelial tumor cell in a medium comprising epidermal growth factor (EGF) and Chang have been discussed in the paragraphs above. These reference do not teach a medium comprising recombinant human epidermal growth

factor (rhEGF) or the basic fibroblast growth factor (bFGF), recombinant human basic fibroblast growth factor (rhbFGF).

However, the Sigma Cell Culture Catalogue teaches the availability of these growth factor supplements at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use rhEGF and rhbFGF to supplement the culture medium. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Ohnuki, Garcia and the Sigma Cell Culture Catalogue to order these supplements and use them in view of the recommended concentrations and practices listed in the technical section of the catalogue.

10. Claims 1-10, 16-22, 33, 34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohnuki et al. (Cancer Research 40:524-534, March 1980), in view Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), Chang (Biochimica et Biophysica Acta 823:161-194, 1986) and Gottlinger et al. (Int. J. Cancer 38:47-53, 1986). The teachings of Ohnuki and Garcia of an immortalized epithelial tumor cell with metastatic potential and Chang have been discussed in the paragraphs above. These reference do not teach a composition comprising the said epithelial tumor cell, nor the said composition comprising a vaccine in combination with a vaccine adjuvant.

However, Gottlinger et al. teach compositions containing epithelial cell surface antigens and *Bordetella pertussis* adjuvant suitable for mounting an immunological response. It would

have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to manufacture a composition comprising the epithelial tumor cell of claim 1 in combination with a *B. pertussis* adjuvant. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of all three references that the production of an adjuvant prepared by culturing autologous epithelial tumor cells coupled with *B. pertussis* adjuvant would be suitable for administration to a non-human animal for augmenting immune responses in order to generate antibodies that would allow one skilled in the art to biochemically characterize a specific antigen defined by the generated antibodies.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703)308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)308-0196.

Alana M. Harris, Ph.D.
Patent Examiner, Group 1642
October 22, 2001

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